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The Antioxidant Axis in Protecting Metabolic and Reproductive Health: Bridging Hepatoprotection, Neuroprotection, and Fertility Restoration

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ABSTRACT

Metabolic disorders such as diabetes, obesity, and metabolic syndrome disrupt systemic homeostasis through persistent oxidative stress, linking hepatic, neurological, and reproductive dysfunction. Oxidative stress arises from an imbalance between reactive oxygen and nitrogen species (ROS/RNS) and endogenous antioxidant defenses, leading to lipid peroxidation, protein oxidation, mitochondrial dysfunction, and inflammation. The liver, as a metabolic hub, becomes particularly vulnerable to ROS-induced fibrosis and lipid dysregulation, while neuronal tissues suffer oxidative neurodegeneration and cognitive decline. Similarly, excessive ROS impairs gametogenesis, hormone synthesis, and fertility in both sexes. Antioxidants play a central protective role by neutralizing ROS, activating endogenous defense systems such as superoxide dismutase, catalase, and glutathione peroxidase, and modulating inflammatory and metabolic pathways. Natural compounds including polyphenols, flavonoids, and vitamins restore redox balance, enhance mitochondrial stability, and prevent fibrotic progression. However, challenges such as poor bioavailability, dose-dependent effects, and individual variability limit clinical translation. Emerging strategies involving nanoformulations, targeted delivery, and integrative therapeutic approaches hold promise for optimizing antioxidant efficacy. Strengthening the antioxidant axis thus represents a unifying therapeutic avenue to protect metabolic, hepatic, neural, and reproductive health, underscoring the pivotal role of redox homeostasis in systemic physiological resilience.

Keywords: Oxidative stress, antioxidants, metabolic health, neuroprotection, reproductive health

INTRODUCTION

Oxidative stress, arising from an imbalance between reactive oxygen species (ROS) generation and antioxidant defense systems, is a central mediator of multiple metabolic and reproductive dysfunctions [1,2]. Chronic conditions such as diabetes mellitus, metabolic syndrome, and obesity exacerbate ROS production, triggering hepatocellular injury, neuronal damage, and impaired fertility [3,4]. The antioxidant axis, comprising endogenous enzymatic defenses, dietary antioxidants, and mitochondria-targeted interventions-plays a pivotal role in counteracting oxidative insults, preserving tissue function, and promoting homeostasis [5,6]. This review provides an integrative perspective on the mechanistic links between oxidative stress, metabolic dysregulation, and reproductive dysfunction, highlighting how antioxidants mitigate liver injury, protect neural integrity, and restore reproductive potential [7,8]. Experimental and clinical evidence support the use of natural compounds, phytochemicals, and targeted antioxidant therapies as adjuncts to conventional management strategies [9,10]. Challenges related to bioavailability, dose optimization, and interindividual variability are also discussed, along with future directions for translational research [11]. Enhancing the antioxidant axis represents a promising multi-targeted approach to improve metabolic, neurological, and reproductive health [12].

Metabolic disorders such as diabetes mellitus, obesity, and metabolic syndrome have become major global health challenges, contributing significantly to morbidity and mortality [1]. These disorders are characterized by chronic hyperglycemia, insulin resistance, dyslipidemia, and low-grade systemic inflammation, which together disrupt metabolic equilibrium and promote multi-organ dysfunction [3]. The liver, brain, and reproductive organs are among the most affected systems, as they are highly dependent on oxidative balance for optimal function [4,13]. Oxidative stress has emerged as a central pathophysiological mechanism that links metabolic dysregulation to cellular and tissue injury [14,15]. It results from an imbalance between the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the capacity of endogenous antioxidant defenses to neutralize them [16]. Under normal physiological conditions, ROS serve as signaling molecules regulating pathways involved in

metabolism, differentiation, and immune response [17]. However, persistent metabolic stress-driven by nutrient overload, mitochondrial dysfunction, and chronic inflammation-leads to uncontrolled ROS and RNS accumulation [18,19]. This oxidative overload damages lipids, proteins, and nucleic acids, initiating a cascade of cellular dysfunction, apoptosis, and inflammation that accelerates the progression of metabolic diseases [20].

Enzymatic antioxidants such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) form the body's first line of defense against oxidative stress [21]. Yet, in metabolic disorders, these systems are often compromised due to glycation, nutrient imbalance, and inflammation, leading to further oxidative imbalance [22]. The liver, as a metabolic hub, becomes particularly susceptible to lipid peroxidation and mitochondrial impairment, while neuronal tissues-owing to their high oxygen consumption and lipid content-suffer oxidative neurodegeneration [23,24]. The reproductive system is also profoundly influenced by oxidative stress [25,26]. In males, elevated ROS levels impair spermatogenesis, disrupt sperm motility, and induce DNA fragmentation, collectively diminishing fertility potential [27]. In females, oxidative stress interferes with follicular development, oocyte maturation, and steroidogenesis, leading to menstrual irregularities and reduced reproductive success [28]. Therefore, understanding oxidative stress as a unifying mechanism of metabolic, hepatic, neurological, and reproductive dysfunction provides a foundation for integrative therapeutic strategies. Strengthening antioxidant defenses through dietary, pharmacological, or lifestyle interventions offers promising avenues to restore redox balance and safeguard systemic health [29,30].

2. Oxidative Stress in Metabolic Dysregulation

2.1 Sources of ROS in Metabolic Disorders

Multiple metabolic pathways contribute to the overproduction of ROS in diabetes and obesity [1,2]. Mitochondrial dysfunction is the primary driver, as excessive glucose and fatty acid oxidation increase the flow of electrons through the electron transport chain [18]. This heightened flux promotes electron leakage and the formation of superoxide radicals, which serve as precursors to other reactive species such as hydrogen peroxide and hydroxyl radicals [20]. Inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), further activate NADPH oxidase (NOX) enzymes, amplifying superoxide production [3]. Hyperglycemia also enhances the polyol pathway, converting glucose to sorbitol and consuming NADPH, a critical cofactor for regenerating reduced glutathione (GSH) [21]. The depletion of NADPH weakens cellular antioxidant capacity. Concurrently, the non-enzymatic glycation of proteins and lipids generates advanced glycation end-products (AGEs), which interact with their receptors (RAGE) to trigger intracellular ROS production and activate pro-inflammatory transcription factors such as NF-κB and MAPK [22]. Collectively, these metabolic and inflammatory mechanisms converge to disrupt redox equilibrium and promote cellular injury [14,15].

2.2 Oxidative Damage and Metabolic Complications

The consequences of sustained oxidative stress are multifaceted, affecting structural and functional components of cells [16,17]. Lipid peroxidation leads to the formation of toxic aldehydes like malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which destabilize membranes and impair cellular signaling [4]. Protein oxidation alters enzyme activity and receptor sensitivity, while oxidative DNA damage and mitochondrial genomes induce mutations, apoptosis, and impaired bioenergetics [23,24]. In hepatic tissue, oxidative stress drives the progression from simple steatosis to steatohepatitis and fibrosis by activating hepatic stellate cells and promoting inflammatory cytokine release [31]. In the brain, ROS disrupts synaptic communication, compromises mitochondrial function, and induces neuronal apoptosis, contributing to cognitive decline and neuropathic complications often observed in diabetic patients [32,33]. Furthermore, oxidative injury to pancreatic β-cells diminishes insulin synthesis and secretion, perpetuating hyperglycemia and metabolic imbalance [34]. Thus, oxidative stress serves not only as a byproduct but as a key pathogenic driver of metabolic disease progression, bridging energy dysregulation, inflammation, and organ-specific dysfunction [35].

3. Hepatoprotective Mechanisms of Antioxidants

The liver plays a central role in energy metabolism, detoxification, and homeostasis, making it highly vulnerable to oxidative stress, especially under diabetic or dyslipidemic conditions [4,31]. Excessive ROS generation in hepatocytes triggers lipid peroxidation, mitochondrial injury, and activation of inflammatory pathways that drive fibrosis and hepatic failure [35]. Natural antioxidants derived from dietary sources and medicinal plants have demonstrated significant hepatoprotective potential through their capacity to neutralize ROS, restore redox balance, modulate inflammation, and improve lipid metabolism [9,10].

3.1 ROS Scavenging

A primary mechanism of hepatoprotection by antioxidants involves direct scavenging of reactive oxygen and nitrogen species [5]. Natural compounds such as polyphenols, flavonoids, carotenoids, and vitamins C and E neutralize free radicals before they can damage cellular macromolecules [7]. For instance, green tea catechins, resveratrol, and curcumin have been shown to reduce hepatic malondialdehyde (MDA) levels a marker of lipid peroxidation, thereby preserving membrane integrity and preventing hepatocyte necrosis [35]. By interrupting the

chain reactions of lipid peroxidation, these compounds protect cellular organelles, stabilize hepatocyte architecture, and improve overall liver function [8].

3.2 Enhancement of Endogenous Antioxidants

Beyond direct scavenging, antioxidants enhance the body's intrinsic defense systems [12]. Compounds such as quercetin, curcumin, and vitamin E activate nuclear factor erythroid 2–related factor 2 (Nrf2), which upregulates the expression of antioxidant enzymes including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) [22]. These enzymes form a coordinated defense network that converts superoxide radicals to hydrogen peroxide and subsequently to water, preventing oxidative injury. The enhancement of glutathione synthesis also helps maintain redox homeostasis, protecting hepatocytes from oxidative and inflammatory insults [26].

3.3 Anti-Inflammatory Effects

Oxidative stress activates redox-sensitive signaling pathways such as NF-κB and MAPK, leading to the production of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 [14]. Antioxidants counteract these effects by inhibiting NF-κB nuclear translocation and suppressing cytokine release [16]. This reduces inflammatory infiltration, limits hepatocyte apoptosis, and mitigates progression toward fibrosis. Curcumin, for example, has demonstrated potent anti-inflammatory effects by blocking NF-κB activation and reducing serum transaminase levels in experimental models of hepatic injury [35].

3.4 Modulation of Lipid Metabolism

Antioxidants also regulate hepatic lipid metabolism, a key factor in preventing steatosis [31]. Activation of AMP-activated protein kinase (AMPK) and modulation of peroxisome proliferator-activated receptors (PPARs) by compounds such as resveratrol and berberine promote fatty acid oxidation while suppressing de novo lipogenesis [32]. This dual action reduces triglyceride accumulation, improves insulin sensitivity, and restores normal hepatic architecture [33].

3.5 Mitochondrial Protection and Anti-Fibrotic Actions

Mitochondrial dysfunction is both a source and a consequence of hepatic oxidative stress [19]. Mitochondria-targeted antioxidants like coenzyme Q10 and mitoquinone (MitoQ) reduce ROS generation at the source, stabilize the mitochondrial membrane potential, enhance ATP production, and limit apoptosis [20,23]. Furthermore, by suppressing the activation of hepatic stellate cells-the main fibrogenic cells of the liver-antioxidants attenuate extracellular matrix deposition, thereby preventing fibrosis progression [24]. Collectively, these mechanisms position antioxidants as promising agents for maintaining hepatic integrity under metabolic stress [34].

4. Challenges and Future Directions

Despite promising preclinical and clinical findings, several challenges continue to limit the full therapeutic potential of antioxidants in protecting metabolic, hepatic, neural, and reproductive health (12). One major limitation lies in the poor bioavailability of many natural antioxidants, resulting from low solubility, rapid metabolism, and limited tissue penetration [29]. These pharmacokinetic barriers reduce their therapeutic concentrations in target organs such as the liver, brain, and gonads [30]. Optimizing delivery systems-including nanoformulations, liposomes, and polymer-based carriers-may enhance stability, absorption, and site-specific targeting [25]. Another critical challenge involves dose optimization [28]. While moderate antioxidant supplementation is protective, excessive doses can paradoxically induce pro-oxidant effects, disrupting redox signaling and cellular homeostasis [13]. Furthermore, individual variability in genetic background, age, comorbidities, and dietary patterns significantly influences antioxidant metabolism and responsiveness, underscoring the need for personalized therapeutic approaches.

Future directions should emphasize integrative strategies that combine antioxidants with metabolic modulators, anti-inflammatory agents, or lifestyle interventions to achieve synergistic effects [4]. Importantly, large-scale, long-term clinical trials are required to establish standardized dosing, safety profiles, and clinical efficacy [6]. Addressing these challenges will be pivotal in translating antioxidant research into practical, evidence-based therapies for metabolic and reproductive health restoration.

CONCLUSION

Oxidative stress is a central mediator of metabolic, hepatic, neural, and reproductive dysfunctions. Enhancing the antioxidant axis through endogenous activation, dietary supplementation, and mitochondria-targeted strategies mitigates hepatocyte injury, preserves neuronal integrity, and restores reproductive potential. An integrated, multi-targeted approach offers promising therapeutic avenues for improving systemic metabolic and reproductive health, emphasizing the central role of redox homeostasis in maintaining organ function and overall physiological resilience.

REFERENCES

1. Guzmán-Carrasco A, Kapravelou G, López-Jurado M, Bermúdez F, Andrés-León E, Terrón-Camero LC, et al. A novel plant-based nutraceutical combined with exercise can revert oxidative status in plasma and liver in a diet-induced-obesity animal model. Antioxidants (Basel). 2024;13(3):274.

2. Ugwu, CE., Sure, SM., Dike, CC., Okpoga, NA and Egba, SI. Phytochemical and *in vitro* antioxidant activities of methanol leave extract of *Alternanthera basiliana*. Journal of Pharmacy Research, 2018; 12(6): 835-839
3. Alum, E.U., Obasi, D.C., Abba, J.N., Aniokete, U.C., Okoroh, P.N., Akwari, A.A. (2025). Evolving Paradigms in Nutrition Therapy for Diabetes: From Carbohydrate Counting to Precision Diets. Obesity Medicine, 2025; 100622. https://doi.org/10.1016/j.obmed.2025.100622
4. Uti, D. E., Atangwho, I. J., Omang, W. A., Alum, E. U., Obeten, U. N., Udeozor, P.A., Agada, S. A., Bawa, I., Ogbu, C. O. Cytokines as key players in obesity low grade inflammation and related complications. Obesity Medicine, Volume 54, 2025,100585. https://doi.org/10.1016/j.obmed.2025.100585
5. Solati A, Taghvimi S, Jamali Z, Vahedi F, Moazamfard M, Bahmyari S, et al. The effect of antioxidants on increased oocyte competence in IVM a review. Reprod Dev Med. 2023; doi:10.1097/rd9.0000000000000063.
6. Cutini M, Bruno C, Mancini A, Balercia G. Antioxidants and male infertility. In: Book Chapter. 2020. doi:10.1007/978-3-030-32300-4_43.
7. Bige O, Gülekli B, Demir A, Gode F, Koçtürk S, Aydiner F, et al. Effect of follicular fluid oxidative stress on subsequent oocyte quality and embryo development. Turkiye Klin J Gynecol Obstet. 2016; doi:10.5336/GYNOBSTET.2014-41089.
8. Hashem R. Oxidative stress statue in follicular fluid of infertile women treated with IVF/ICSI-ET. J Global Pharma Technol. 2018.
9. Bansal AK. Role of oxidative stress, reactive oxygen species & antioxidants in male reproductive functions. Theriogenology Insight. 2019; doi:10.30954/2277-3371.01.2019.7.
10. Bulama I, Suleiman N, Bilbis LS, Abbas AY, Jinjiri N, Saidu Y, et al. Antioxidative and neurotherapeutic effect of ascorbic acid on albino rats induced with traumatic brain injury. JCNOS. 2020; doi:10.37212/JCNOS.800233.
11. Prasad KN. Neuroprotection by micronutrients and cannabidiol (CBD) in neurodegenerative diseases. JBN. 2020;1:103.
12. Egba, S.I., Ademola C F and Omoruyi L E (2021) Bucholzia coriacea seed extract attenuates mercury induced cerebral and cerebellar oxidative neurotoxicity via NO signalling and suppression of oxidative stress, adenosine deaminase and acetylcholinesterase activities in rats. Avicenna J Phytomed. 2022 Jan-Feb;12(1):42-53. doi: 10.22038/AJP.2021.18262. PMID: 35145894; PMCID: PMC8801217.
13. Salvagno M, Sterchele ED, Zaccarelli M, Mrakic-Sposta S, Welsby IJ, Balestra C, Taccone FS. Reactive oxygen species ROS reactive nitrogen species RNS antioxidants and cerebral vascular tone. Preprint. 2024; doi:10.20944/preprints202401.0682.v1.
14. Egba, S Ikechukwu, Okonkwo C Onyinye, Ogbodo J Onyebuchi and Ezeh V Nzubechukwu Neuroprotective Potentials of *Alstonia boonei* extracts on Biochemical Markers of Brain Integrity in Experimental Rats, Trop J Nat Prod Res, 2021; 5(6): 1106-1109. doi.org/10.26538/tjnpr/v5i6.21
15. Alum, E.U., Uti, D.E. & Offor, C.E. Redox Signaling Disruption and Antioxidants in Toxicology: From Precision Therapy to Potential Hazards. *Cell Biochem Biophys* (2025). https://doi.org/10.1007/s12013-025-01846-8
16. Escribano-López I, Díaz-Morales N, Iannantuoni F, López-Domènech S, de Marañón AM, Abad-Jiménez Z, et al. The mitochondria-targeted antioxidant MitoQ modulates oxidative stress, inflammation and leukocyte-endothelium interactions in leukocytes isolated from type 2 diabetic patients. Redox Biol. 2016;10:200-205.
17. Rossman MJ, Santos-Parker JR, Steward CAC, Bispham NZ, Cuevas LM, Rosenberg HL, et al. Chronic supplementation with a mitochondrial antioxidant (MitoQ) improves vascular function in healthy older adults. Hypertension. 2018;71(4):637-645.
18. Zozina VI, Covantev S, Goroshko OA, Krasnykh LM, Kukes VG. Coenzyme Q10 in cardiovascular and metabolic diseases: current state of the problem. Curr Cardiol Rev. 2018;14(3):164-174.
19. Sharifi-Rigi A, Siri M, Abazari O, Dastghaib S, et al. Coenzyme Q10 a key antioxidant in the management of diabetes-induced cardiovascular complications—an overview of mechanisms and clinical evidence. Int J Endocrinol. 2024;2024:2247748.
20. Izah, S.C., Betiang, P.A., Ugwu, O.P.C., Ainebyoona, C., Uti, D.E., Echegu, D.A., Alum, B.N. The Ketogenic Diet in Obesity Management: Friend or Foe?. *Cell Biochem Biophys* (2025). https://doi.org/10.1007/s12013-025-01878-0
21. Mason SA, Wadley GD, Keske MA. Effect of mitochondrial-targeted antioxidants on glycaemic control cardiovascular health and oxidative stress in humans a systematic review and meta-analysis. Diabetes Obes Metab. 2022; doi:10.1111/dom.14669.

22. Obasi, D.C., Abba, J.N., Aniokete, U.C., Okoroh, P.N., Akwari, A.A. (2025). Evolving Paradigms in Nutrition Therapy for Diabetes: From Carbohydrate Counting to Precision Diets. Obesity Medicine, 2025; 100622. https://doi.org/10.1016/j.obmed.2025.100622
23. Karakoc M, Ozmen O, Zengin G, Ciftci H. Oleuropein attenuated docetaxel-induced liver and kidney toxicity in rats by modulating oxidative stress gene expressions and histopathological damage. Pak J Pharm Sci. 2025;38(5): doi:10.36721/PJPS.2025.38.5.REG.12955.1.
24. Tian T, Li L, Liu X, Xiang Y, Li Y, Li Z, et al. Multistage countercurrent extraction of abalone viscera oil and its hypolipidemic action on high-fat diet-induced hyperlipidemia mice. Nutrients. 2025;17(19):3062.
25. Martínez-Ruiz A, Badia J, Baldomà L. Extracellular vesicles from probiotics: A novel approach to functional foods. Nutrients. 2025;17(19):3066.
26. Jakimiuk A. A comprehensive review of robinetin distribution biological activity and pharmacokinetic parameters. Int J Mol Sci. 2025;26(19):9546.
27. Yaikwawong P, Kamdee K, Chuengsamarn S. Curcumin attenuates liver steatosis via antioxidant and anti-inflammatory pathways in obese patients with type 2 diabetes mellitus a randomized controlled trial. Int J Mol Sci. 2025;26(19):9286.
28. Dillard DM. Phytotherapeutic support for infertility evaluating the evidence. In: Book Chapter. 2022; doi:10.1016/b978-0-12-818309-0.00010-1.
29. Chen Y, Feng X, Hu X, Sha J, Li B, Zhang H, et al. Dexmedetomidine ameliorates acute stress-induced kidney injury by attenuating oxidative stress and apoptosis through inhibition of the ROS/JNK signaling pathway. Oxid Med Cell Longev. 2018;2018:4035310.
30. Wang Y, Hao L, Wang T, Liu W, Chen X, Li Y, et al. Synergistic hepatoprotective effects of schisandrin B and glycyrrhizic acid against carbon tetrachloride-induced hepatotoxicity in rats. Drug Des Devel Ther. 2019;13:1169-1178.
31. Zhang H, Davies KJA, Forman HJ. Oxidative stress response and Nrf2 signaling in aging. Free Radic Biol Med. 2015;88(Pt B):314-336.
32. Izah SC, Uti DE, Ugwu OP, Betiang PA, Basajja M, Ejemot-Nwadiaro RI. Targeting Cellular Senescence for Healthy Aging: Advances in Senolytics and Senomorphics. Drug Des Devel Ther. 2025 Sep 19;19:8489-8522. doi: 10.2147/DDDT.S543211. PMID: 40994903
33. Alum EU, Uti DE, Egba SI, Ugwu OP-C, Aja PM. The Role of Phytochemicals in Age-Related Cognitive Decline: A Natural Solution for Brain Health. *Natural Product Communications.* 2025;20(6). doi:10.1177/1934578X251350761
34. Hussain T, Tan B, Yin Y, Blachier F, Tossou MC, Rahu N. Oxidative stress and inflammation: what polyphenols can do for us? Oxid Med Cell Longev. 2016;2016:7432797.
35. Ogugua, Victor N., Njoku, Obioma U., Egba, Simeon I., Uroko, Robert I and Ignatius Glory. In vitro study of nutritional and antioxidant properties of methanol extract of *Nauclea latifolia* root bark. Biomedical Research, 2018; 29(21): 3766-3773

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